II. REMARKS

Claims 1 to 33 are pending. A marked up version showing the amendments to the specification and the claim is attached hereto as Exhibit A.

A. Regarding the Amendments

The specification has been amended to preserve the proprietary nature of the trademarked term "Sepharose" by using the term as an adjective to refer to a "gel" matrix. As such, the amendment merely addresses a formality and does not add new matter.

Claim 16 has been amended to correct a typographical error. As such, the amendment does not add new matter.

B. Regarding the Species Election

It is stated in the Office Action that a search of the various sequences disclosed in the subject application would constitute an undue search burden given the ever-increasing size of the databases and, therefore, the species election has been made final. As discussed below, the issue as to whether a search would constitute an undue burden is not the standard for requiring a species election. Nevertheless, Applicants maintain that a requirement of separate searches for each of the sequences in separate patent applications would constitute a far greater burden on U.S. Patent Office resources, including clerical and examination resources, than would a search by the Examiner of all of the sequences in the subject application. As was previously pointed out, the substantial sequence homology would necessarily result in a search of art relevant to any one of the sequences being relevant to each and every one of the other sequences. As such, the requirement that each of the various promyostatin (GDF-8) polypeptides be examined in separate applications cannot be justified given the substantial sequence homology shared among the sequences and the substantial duplication of effort that would be required for the U.S. Patent Office to search each sequence in separate applications.

Notwithstanding the above reason for removing the species election requirement, Applicants point out that the standard for determining whether various species should be examined together is not whether the search would be a burden but, instead, is whether the species share a "commonality of operation, function and effect" (MPEP § 806.04(e)). As disclosed in the specification, the promyostatin polypeptides share a commonality of operation, function and effect and, therefore, properly should be examined together. Similarly, each of the peptide portions of promyostatin share a commonality of operation, function and effect, including, for example, the mature C-terminal portion, which has myostatin activity, and the prodomain, which can inhibit the ability of myostatin to activate signal transduction (see, for example, Example 7, pages 105-106). Accordingly, Applicants respectfully request that the Examiner withdraw the species election requirement and examine the sequences together.

Applicants also point out that, as set forth in the handout provided at the November 15, 2001, PTO Customer Partnership meeting for Bio/Chemical Practitioners, in the section entitled "Restriction Practice", "allowable linking claims(s) requires withdrawal of restriction as to any claim(s) depending from or otherwise including all of the limitations of the allowable linking claim" (see Exhibit B, copy of above-mentioned section entitled "Restriction Practice"; page 1, third panel). Applicants point out that claim 1 of the subject application is a genus claim linking species claims. As indicated in Exhibit B (page 2, third panel), if claim 1 is determined allowable, all of the inventions become subject to examination (i.e., all of the polynucleotide encoding the disclosed GDF-8 polypeptides of the subject application). For the reasons set forth below, it is submitted that claim 1 is allowable and, therefore, it is respectfully requested that the Examiner rejoin and examine each of the polypeptide species as set forth in the claims.

C. Regarding the Specification

The specification is objected to for using the term "Sepharose" without preserving the proprietary nature of the trademark. The specification has been amended to address this informality. As such, it is respectfully requested that the objection be withdrawn.

D. Double Patenting Rejection

The rejection of claims 1 to 3 under the judicially established doctrine of obviousness-type double patenting over claim 1 of U.S. Pat. No. 5,827,733 is respectfully traversed.

Applicants recognize the potential overlapping subject matter, but respectfully defer responding to this ground of rejection until a notice is received that the claims in the subject application are otherwise in condition for allowance.

E. Rejections under 35 U.S.C. § 112

The objection to the specification and corresponding rejection of claims 1 to 3, 8 to 12 and 14 to 17 35 U.S.C. § 112, first paragraph, as allegedly lacking an adequate written description are respectfully traversed.

It is stated in the Office Action that the specification discloses that the C-terminal region of myostatin can interact with its receptor and affect signal transduction, and that the prodomain of promyostatin can interact with the mature or parent protein. It is alleged, however, that the disclosure of these two regions is not sufficient to define the claimed genus, which encompasses subgenera of molecules having diverse functions and, therefore, diverse functional requirements (Office Action, page 4). It is stated, for example, that no structural characteristics or sequences required for any particular function have been set forth, and that there is no description of features that would be required for activators, inhibitors or other molecules.

Applicants point out, however, that the specification discloses three regions of a promyostatin polypeptide, including a signal peptide (about amino acid residues 1 to 20), a prodomain (about amino acid residues 20 to 262), and a mature C-terminal domain (myostatin; about amino acid residues 267 to 375), and further discloses such regions in promyostatin polypeptides expressed in various vertebrate species, including, for example, murine and bovine species and humans (see page 22, line 8 to page 23, line 13; and page 32, lines 20-29). As such, the specification discloses the regions of promyostatin associated with specific functions (see, for example, page 21, lines 6-27).

The specification also discloses that a peptide comprising the C-terminal portion of promyostatin specifically binds to the activin receptor (Example 7, page 105, lines 3-26), and further provides an assay for detecting such specific binding, which one skilled in the art would recognize as useful for identifying additional peptide portions of promyostatin having such an activity (see, also, Example 9, pages 107-109). In view of this disclosure, the skilled artisan would have known that Applicants were in possession of peptide portions of promyostatin that can activate myostatin signal transduction.

The specification also discloses that a peptide comprising the prodomain of promyostatin inhibits myostatin binding to activin receptor (Example 7, page 105, line 27, to page 106, line 2) and, therefore, is an inhibitor of myostatin signal transduction. In addition, the skilled artisan would have known that the assay as disclosed in Example 7 can be used to identify other peptide portions of promyostatin that inhibit myostatin signal transduction. The specification further discloses mutant promyostatin polypeptides that are not susceptible to proteolytic cleavage, or example, promyostatin polypeptides having a mutation in the proteolytic cleavage site, resulting in a polypeptide that cannot be cleaved to generate an active myostatin polypeptide and that can have dominant negative activity (see page 33, line 26, to page 34, line 5). As such, it is submitted that one skilled in the art would have known that Applicants were in possession of promyostatin polypeptides and peptide portions thereof that can inhibit myostatin signal transduction.

The specification also discloses additional molecules involved a myostatin signal transduction pathway, including, for example, the Smad proteins, and further discloses that the phosphorylation state of the Smad proteins is dependent on myostatin signal transduction (see page 44, lines 8-21). As such, the skilled artisan would have known that, in addition to the activin receptor binding assay described in Example 7, an assay based on a determination of Smad phosphorylation state can be used to identify a peptide portion of a promyostatin polypeptide that can affect myostatin signal transduction.

In summary, the specification discloses peptide portions of promyostatin that can activate or that can inhibit myostatin signal transduction, exemplifies such peptides in promyostatin polypeptides

from various vertebrate species, and provides assays that, as disclosed in the specification, can identify peptide portions of a promyostatin polypeptide that can affect myostatin signal transduction. As such, it is submitted that specification adequately describes the claimed subject matter such that one skilled in the art would have known that the Applicants were in possession of the invention. Accordingly, it is respectfully requested that the objection to the specification be withdrawn and that the corresponding rejection of the claims as allegedly lacking an adequate written description be removed.

The objection to the specification and corresponding rejection of claims 1 to 3, 8 to 12 and 14 to 17 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement are respectfully traversed.

It is acknowledged in the Office Action that the specification enables mature myostatin proteins and the promyostatin proregion. It is alleged, however, that the specification does not enable all functional peptide portions of a promyostatin polypeptide encompassed within the claims. It is stated, for example, that the claims encompass "all "peptide portions", which are defined by Applicant as having many different functions." (Office Action, paragraph bridging pages 5-6). Applicants point out, however, that, while a peptide portion of promyostatin can act in various ways, the "function" of the claimed peptides is specifically defined as "having or affecting an activity associated with the stimulation or inhibition ... myostatin signal transduction activity..." and the specification provides examples of such a function can be effected (page 21, lines 6-17). Thus, while a peptide of the invention can act in various ways to cause diverse effects, the function is clearly defined. In this respect, the specification provides specific examples of such peptides that can activate or inhibit myostatin signal transduction, and further provides routine assays for determining that a peptide portion of promyostatin can have or affect an activity associated with the stimulation or inhibition of myostatin signal transduction.

It is also stated in the Office Action that, while synthetic and recombinant techniques are available, it is not routine in the art to screen large numbers of peptides where the expectation of

obtaining the desired activity is unpredictable (Office Action, sentence bridging pages 5-6). Applicants are unaware of the basis for correlating an expectation of obtaining a peptide having a desired activity with whether a screening assay is deemed to be routine. Indeed, methods of screening randomly generated molecules to identify those that bind a particular receptor or have a desired activity are well known and routine in the art.

It is well recognized that undue experimentation is not necessarily correlated to how much work may be necessary, and that "a considerable amount of experimentation is permissible if it is merely routine...." (see In re Wands 8 USPQ2d, 1400 (Fed. Cir. 1988, at 1404; citing In re Jackson 217 USPQ 804 (Bd. App. 1982), at 807). In the present case, the exemplified activin receptor screening assay (Example 7) can be performed as a matter of routine. As such, in view of Applicants' disclosure that specific peptide portions of promyostatin are associated with the ability to activate or inhibit myostatin signal transduction, it is submitted that no more than routine experimentation using methods and peptide portions of promyostatin as disclosed in the specification would have been required for the skilled artisan to make various and numerous peptide portions of promyostatin and examine such peptides for the ability to affect myostatin signal transduction.

As such, in view of the exemplified functional peptide portions of promyostatin and the methods for determining whether a peptide activates or inhibits myostatin signal transduction, it is submitted that undue experimentation would not have been required for one skilled in the art to make and use the claimed peptides. Accordingly, it is respectfully requested that the objection to the specification be withdrawn and corresponding rejection of the claims as allegedly lacking enablement be removed.

The rejection of claims 1 to 3, 8 to 12 and 14 to 17 under 35 U.S.C. § 112, second paragraph, as allegedly failing to particularly point out and distinctly claim the subject matter of the invention is respectfully traversed.

It is alleged in the Office Action that the terms "peptide portions", "functional peptide portions" and "proteolytic fragments" are indefinite because the specification does not define the

limits of such portions or fragments and because there is no definition of "functional." As such, it is alleged that one skilled in the art would not know what molecules meet the limitations of the claims.

Applicants point out that the terms "peptide portion" and "proteolytic fragment" are defined at page 18, lines 4-28, and, as was pointed out with respect to the "written description" rejection, the term "functional peptide portion", when used with respect to a promyostatin polypeptide, is defined at page 21 (see lines 6-16) of the specification, wherein it is "characterized, in part, by having or affecting an activity associated with the stimulation or inhibition of GDF signal transduction" and, more specifically, myostatin signal transduction (see, also, page 43, 16-28). Thus, the specification clearly defines the terms as used in the claims, and further provides examples of methods for determining whether a peptide portion of a promyostatin polypeptide has a function related to myostatin signal transduction (see Examples 7 and 9, demonstrating, for example, myostatin binding to the activin receptor and inhibition of such binding by the promyostatin prodomain peptide).

As such, it is submitted that the skilled artisan, reading the claims in view of the specification, would know the subject matter encompassed within the claims. Accordingly, it is respectfully requested that this rejection of the claims under 35 U.S.C. § 112, second paragraph, be removed.

The rejection of claims 16 and 17 under 35 U.S.C. § 112, second paragraph, as allegedly failing to particularly point out and distinctly claim the subject matter of the invention is respectfully traversed.

It is stated in the Office Action that claims 16 and 17 recite the term "functional peptide portion of", whereas the term "functional peptide portion thereof" likely should have been recited. Claim 16 has been amended to correct this typographical error. However, claim 17 appears to correctly recite the term "thereof" and, therefore, has not been amended. Accordingly, it is respectfully requested that this rejection of the claims under 35 U.S.C. § 112, second paragraph, be removed.

No fee is deemed necessary in connection with the filing of this Amendment. However, if any fee is required, the Commissioner is authorized to charge any fee (or credit any overpayment) to Deposit Acct. No. 50-1355.

The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this application.

Respectfully submitted,

Dated: January 29, 2002

Lisa A. Haile, J.D., Ph.D.
Reg. No. 38,347
Telephone: (858) 677-1456
Facsimile: (858) 677-1465

Customer Number: 28213
GRAY CARY WARE & FREIDENRICH LLP
4365 Executive Drive, Suite 1100
San Diego, CA 92121-2133

Encls. Exhibits A and B

EXHIBIT A

MARKED UP VERSION SHOWING THE AMENDMENTS TO THE SPECIFICATION AND THE CLAIM

A. In the Specification

The paragraph bridging pages 88-89 was amended by adding the term "gel", as shown by the underlining (Note: the underlining of the reference in the following paragraph was in the application as filed, and is not an indication that the reference was added by the present amendment)

Monoclonal antibodies can be isolated and purified from hybridoma cultures by a variety of well established techniques, including, for example, affinity chromatography with Protein-A SEPHAROSE gel, size exclusion chromatography, and ion exchange chromatography (Coligan et al., *supra*, 1992, see sections 2.7.1-2.7.12 and sections 2.9.1-2.9.3; see, also, Barnes et al., "Purification of Immunoglobulin G (IgG)," in Meth. Molec. Biol. 10:79-104 (Humana Press 1992), which is incorporated herein by reference). Methods of *in vitro* and *in vivo* multiplication of monoclonal antibodies is well known to those skilled in the art. Multiplication *in vitro* can be carried out in suitable culture media such as Dulbecco's Modified Eagle Medium or RPMI 1640 medium, optionally replenished by a mammalian serum such as fetal calf serum or trace elements and growth sustaining supplements such as normal mouse peritoneal exudate cells, spleen cells, bone marrow macrophages. Production *in vitro* provides relatively pure antibody preparations and allows scale-up to yield large amounts of the desired antibodies. Large scale hybridoma cultivation can be carried out by homogenous suspension culture in an airlift reactor, in a continuous stirrer reactor, or in immobilized or entrapped cell culture. Multiplication *in vivo* can be carried out by injecting cell clones into mammals histocompatible with the parent cells, for example, syngeneic mice, to cause growth of antibody producing tumors. Optionally, the animals are primed with a hydrocarbon, especially oils such as pristane (tetramethylpentadecane) prior to injection. After one to three weeks, the desired monoclonal antibody is recovered from the body fluid of the animal.

The paragraph at page 103, lines 6-16, was amended as follows:

In order to elucidate the biological activity of myostatin, large quantities of myostatin protein were purified for bioassays. Stable Chinese hamster ovary (CHO) cell lines producing high levels of myostatin protein were generated by co-amplifying a myostatin expression cassette with a dihydrofolate reductase cassette using a methotrexate selection scheme (McPherron et al., *supra*, 1997). Myostatin was purified from the conditioned medium of the highest producing line by successive fractionation on hydroxyapatite, lentil lectin SEPHAROSE gel, DEAE agarose, and heparin SEPHAROSE gel. Silver stain analysis revealed that the purified protein obtained following these four column chromatography steps (referred to as "heparin eluate") consisted of two species with molecular masses of approximately 35 kilodaltons (kDa) and 12 kDa.

B. In the Claims

Claim 16 was amended as follows:

16. (Amended) The peptide of claim 8, wherein the peptide is a mature myostatin comprising about amino acid residues 268 to 374 of a promyostatin polypeptide, or a functional portion [of] thereof.

RESTRICTION PRACTICE

POLYNUCLEOTIDES
POLYPEPTIDES
AND FRAGMENTS

Christopher Low / James Housel
TC1600 /AU 1653 (703) 308-2923
christopher.low@uspto.gov

Official Gazette, 1192 O.G. 68 (Nov 19, 1996)

"Nucleotide sequences encoding different proteins are structurally distinct chemical compounds and are unrelated to one another. These sequences are thus deemed to normally constitute independent and distinct inventions within the meaning of 35 U.S.C. 121".

"Absent evidence to the contrary, each such nucleotide is presumed to represent an independent and distinct invention, subject to a restriction requirement pursuant to 35 U.S.C. 121 and 37 CFR 1.141".

"In some exceptional cases, the complex nature of the claimed material may necessitate that the reasonable number of sequences to be selected be less than 10".

"In other cases, applicants may petition pursuant to 37 CFR 1.181 for examination of additional nucleotide sequences by providing evidence that the different nucleotide sequences do not cover independent and distinct inventions".

Official Gazette, 1192 O.G. 68 (Nov 19, 1996)

- Limited to expressed sequence tags (ESTs).
- Polypeptides specifically not recited. One polypeptide per application.
- Burden placed at up to ten (10) sequences.

Current Practice

- All polynucleotides (DNA, RNA, and oligonucleotides).
- No change to practice of one polypeptide per application.
- Burden significantly increased. Number of sequences decreased, often to one (1) sequence and indistinct fragments thereof.

Linking Claims

- Restriction requirement is subject to nonallowance of the linking claim(s).
- Allowable linking claim(s) requires withdrawal of restriction as to any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s).
- Linking claims assessed on basis of 35 U.S.C. 101, 112, 102, and 103.

Linking Claims (MPEP §809.03)

Common types of linking claims which, if allowed, act to prevent restriction between inventions that can otherwise be shown to be divisible:

- Genus claims linking species claims
- Claims to the necessary process of making a product linking proper process and product claims
- Claims to "means" for practicing a process linking proper apparatus and process claims
- Claims to a product, linking claims to a process of making, and claims to a method of use of the product

Linking Claims

Common biotech example:

Claim 1. An isolated polynucleotide having antisense activity against SEQ ID NO:1.

Claim 2. The isolated polynucleotide of claim 1 selected from the group consisting of any one of SEQ ID NO: 2-125.

Linking Claims

- Claim 1 is a linking claim because it links each of inventions of SEQ ID NOs:2-125 together.
- Election of one of SEQ ID NOs:2-125 is required.
- Claim 1 examined with the elected invention.
- If claim 1 is allowable, all of inventions of SEQ ID NOs:2-125 become subject to examination.
- If claim 1 is not allowable, then only the elected invention is examined.

Linking Claims and Lack of Unity

- Consistent examination
- Consistent treatment of claims
- Consistent restriction practice

EnD

- This is a placeholder slide. It will disappear from the presentation.